CLINICAL, IMMUNOLOGICAL AND VIROLOGICAL INDICATORS OF ANTIRETROVIRAL THERAPY EFFICIENCY

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Antiretroviral therapy (ART) for HIV-positive patients allowed labeling the disease a therapeutically controlled one. The main goal of ART is to prolong patient's life and preserve its quality. This is accomplished through viral load reduction (decrease of the number of HIV-RNA copies in blood plasma), which leads to the growing numbers of CD4+-T-lymphocytes. However, ART can be ineffective. In 2010–1014, we conducted an observational cohort retro/prospective study aimed at learning how often ART can be ineffective from immunological (II), virological (VI) and clinical points of view. The study was carried out at the premises of the Republic Center of AIDS and Infectious Diseases (Kazan, Russia). The study included 341 adult HIV-positive patients subjected to ART at 3rd and 4th stages of disease's development, with the treatment virologically efficient at least during the first year. The observation period was 1 to 3 years. ART was considered II (immunologically inefficient) when the number of CD4+ increased for less than 50 cells/mcl through the year with HIV completely suppressed. VI (virological inefficiency) of ART was registered if the number of HIV RNA copies was above the definition threshold after 6 months of treatment. ART was II in 14.0–15.9 % of cases after a year of treatment and in 22 % of cases after three years. It was noted that subsequent restoration of an adequate number of T-lymphocytes CD4+ required they overcame the threshold of 100 cells/mcl within the 1st year of treatment. Virologically, ART was effective for 92.7 % for patients. Most (80 %) cases of VI of ART were results of patients' lax attitude towards treatment. Clinically, ART helped 91 % of patients; this result largely depended on the number participants for whom ART was II. II of ART is a risk factor, the risk being progression of the disease with active ART in the background and death of the HIV-positive individual. II of ART makes the risk of clinical progression of HIV 6.232 times higher (95 % CI 3.106–12.51).

Keywords: HIV, antiretroviral therapy, clinical efficacy, virological efficacy, immunological efficacy, therapy failure

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КЛИНИКО-ИММУНОЛОГИЧЕСКИЕ И ВИРУСОЛОГИЧЕСКИЕ ПОКАЗАТЕЛИ ЭФФЕКТИВНОСТИ АНТИРЕТРОВИРУСНОЙ ТЕРАПИИ

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Применение антиретровирусной терапии (АРВТ) при ВИЧ-инфекции позволило перевести заболевание в разряд терапевтически контролируемых. Основная цель АРВТ — увеличение продолжительности жизни пациента и сохранение ее качества. Она достигается снижением вирусной нагрузки (числа копий РНК ВИЧ в плазме крови), что приводит к росту числа CD4+-Т-лимфоцитов. Но терапия может быть неэффективной. В работе изучена частота случаев иммунологической (ИН), вирусологической (ВН) и клинической неэффективности АРВТ. В исследование включили 341 взрослого ВИЧ-инфицированного пациента, получавшего АРВТ, начатую на стадиях 3–4 заболевания, с вирусологической эффективностью как минимум в течение первого года лечения. Участников исследования наблюдали на протяжении 1–3 лет. ИН АРВТ определяли как увеличение числа клеток CD4+ менее чем на 50 клеток/мкл в год на фоне полной супрессии ВИЧ, ВН АРВТ — как число копий РНК ВИЧ выше порога определения через 6 мес от начала лечения. Частота случаев ИН АРВТ составила 14,0–15,9 % для одного года лечения и 22 % для трех лет наблюдений. Отмечено, что для последующего адекватного восстановления содержания Т-лимфоцитов CD4+ необходимо увеличение их числа в первый год терапии более чем на 100 клеток/мкл. Вирусологически эффективной АРВТ была для 92,7 % пациентов. Большая часть (80 %) случаев ВН АРВТ была обусловлена низкой приверженностью пациентов к лечению. Клиническая эффективность АРВТ составила 91 % и в значительной степени определялась числом участников исследования с ИН АРВТ. Иммунологическая неэффективность АРВТ является фактором риска прогрессирования заболевания на фоне АРВТ и смерти при ВИЧ-инфекции. Риск клинического прогрессирования ВИЧ-инфекции при ИН АРВТ выше в 6,232 раз (95 % ДИ 3,106–12,51).

Ключевые слова: ВИЧ-инфекция, антиретровирусная терапия, клиническая эффективность, вирусологическая эффективность, иммунологическая эффективность, неэффективность терапии

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The main goal of ART is to prolong patient's life and preserve its quality. Clinical ineffectiveness (CI) of ART results in development of a new opportunistic infection in the patient's body after 3–6 months of treatment. Thus, it takes a long-term study to evaluate effectiveness of ART.

Important aspects of ART that determine the rate of HIV-positive patients survival are virological and immunological responses to the therapy. From the virus control point of view, the task is to minimize the viral load in the patient's body (preferably to below 50 RNA copies/ml) and hold it there as long as possible to stop progression of the disease and prevent development of viral resistance to drugs. Virological ineffectiveness (VI) of ART increases the risk of HIV progression in several times [1, 2]. Immunologically, ART is successful when the number of CD4+ T-lymphocytes is growing (the growth is significantly more intensive with the full viral suppression). Immunological ineffectiveness (II) of ART is observed in approximately 15 % of patients [3]: they suffer from immunodeficiency for a long time despite taking antiretroviral drugs, which increases the risk of development of AIDS- and non-AIDS-defining diseases [4].

The aim of our study was to assess the incidence of clinical, virological and immunological inefficiency of ART and determination of conditions ensuring effectiveness of ART.

METHODS

The observational cohort retro/prospective study was conducted in 2010–2014 at the premises of the Republic Center of AIDS and Infectious Diseases Prevention and Treatment, Kazan (hereinafter — AIDS Center). The study was approved by the local ethics committee (Protocol 3 dated March 24, 2015).

Data used in the study described adult patients with a confirmed HIV-positive status that were in the dispensary observation at the AIDS Center in 1999–2014. Criteria for inclusion were as follows: 1) ART receiver for more than a year, HIV RNA in blood plasma below the registration threshold after 6 months from ART start and (minimum) during the first year; 2) ART started at stages 3–4 as defined by the clinical classification of HIV approved by the Health and Human Services Ministry of the Russian Federation by Order No. 166 dated 17.03.2006. Criteria for exclusion were: 1) underage; 2) ART reception for less than one year; 3) registered HIV RNA in plasma after 6 months of ART; 4) HIV in incubation, primary symptoms and terminal stages; 5) receiving both ART and antiviral therapy against viral hepatitis. Criteria for early retirement from the study were:1) cessation of ART; 2) registered viral load (HIV RNA content) that developed after the earlier achieved suppression of HIV in plasma (to determine the immunological effectiveness of ART); 3) start of viral hepatitis antiviral therapy while receiving ART; 4) death of the patient. All patients signed informed consent to examination and ART application.

The number of observed patients was 341,204 of them were male. The age of the participants was 35 (32; 40) (hereinafter, data describing the sample are given as median and interquartile range). 59.2 % of cases were parenteral infection. The participants were registered at the AIDS center for 5 years (2; 9) before treatment. Shares of HIV stages among participants: stage 3 — 34.6 %, 4A — 29.9 %, 4B — 28.4 %, 4C — 7.1 %. Content of T-lymphocytes CD4+ in peripheral blood prior to ART: 186 (120; 277) cells/μL; content of HIV RNA in plasma: 93,000 (22,750; 280,625) copies/ml.

All patients were prescribed ART in accordance with methodological recommendations issued by the Health and Human Services Ministry of the Russian Federation, 7125-RKh dated 29.12.2006, observation period — 1 to 3 years. The first line ART regimen included two nucleoside reverse transcriptase inhibitors (NRTI), the third component was non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) or integrase inhibitor (INI) (Fig. 1).

Immunological effectiveness of ART was evaluated by the increase in the number of CD4+ T-lymphocytes. The patients were divided into two groups: 1) those with an increase of less than 50 cells/μL in a year (no response to therapy); 2) those with an increase of more than 50 cells/μL in a year. Content of CD4+ T-lymphocytes was measured at least twice, time between measurements — 3 months. This was done to eliminate random error due to variability of absolute values of the indicator.

Virological effectiveness of ART was evaluated no earlier than in the second year of treatment because undetectable viral load during the first year of treatment was an inclusion criterion. VI of ART was acknowledged if the number of HIV RNA increased over 400 copies/ml up to 2010 and over 150 copies/ml in the following years. Short-term rise in the level

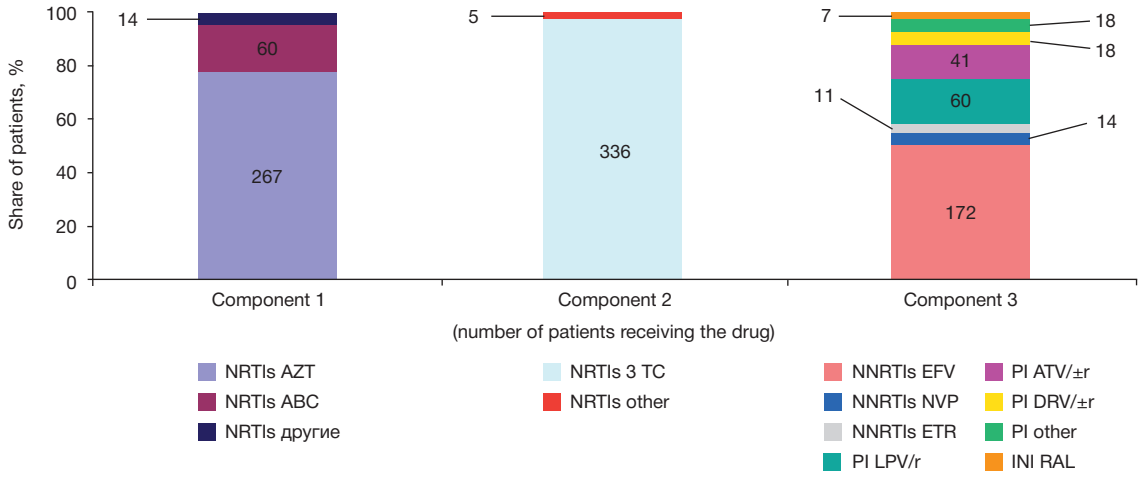

Fig. 1. Groups of patients by type of drug, three-component first line ART

NRTIs — nucleoside reverse transcriptase inhibitor; NNRTI — non-nucleoside reverse transcriptase inhibitor; PI — protease inhibitor; INI — integrase inhibitor; AZT — azidothymidine; ABC — abacavir; other NRTIs — stavudine, didanosine, phosphazide; 3TC — lamivudine; EFV — efavirenz; NVP — nevirapine; ETR — etravirine; LPV/r — lopinavir boosted with ritonavir; ATV/±r — atazanavir boosted/not boosted with ritonavir; DRV/±r — darunavir boosted/not boosted with ritonavir; other PI — fosamprenavir, saquinavir, indinavir, nelfinavir, ritonavir; RAL — raltegravir.

of HIV RNA — less than 1000 copies/ml, a "blip", — was not considered a sign therapy ineffectiveness.

CI of ART was acknowledged if a new opportunistic infection developed in the patient's body after 3–6 months of treatment. Inflammatory syndrome accompanying immune system reconstitution was not considered a sign of therapy ineffectiveness.

Content of $CD4^+$ T-lymphocytes and HIV RNA was measured before the start of ART, after 6 and 12 months after start of ART, further on — annually throughout the treatment period. Quantification of HIV RNA in plasma was performed through polymerase chain reaction in real time using Cobas Amplicor HIV-1 Monitor v.1.5 (Hoffman-La Roche, Switzerland) and LCx HIV RNA Quantitative assay (Abbott Laboratories, USA) tests in COBAS TaqMan 48 (Hoffman-La Roche) and Abbott m2000rt (Abbott Molecular, USA) analyzers with the sensitivity threshold of 400 copies/ml up to 2010 and 150 copies/ml for the following years. HIV resistance to antiretroviral drugs was determined by sequencing using ViroSeq HIV-1 Genotyping System test (Applied Biosystems, USA) with Applied Biosystems 3100 and 3130 analyzers (Applied Biosystems). The number of $CD4^+$ T-lymphocytes was determined by flow cytometry using monoclonal antibodies (mAbs). Lymphocytes phenotyping was performed by direct immunofluorescence with Multitest 6-color TBNK Reagent (Becton Dickinson, USA) containing MAb $CD3^+$, $CD4^+$, $CD8^+$, $CD16/56^+$, $CD19^+$, with account of immunofluorescence reaction in FACScanto II flow cytometer (Becton Dickinson).

A factor's influence (II of ART) on the treatment outcome (HIV disease progression, death) was measured for the entire period of therapy regardless of the time the factor appeared.

Statistical analysis of the results was performed using the methods of descriptive and comparative statistics and programs STATISTICA 10.0 (StatSoft, USA), Microsoft Excel 2003, OpenEpi 3.01 [5]. Normality of distribution was assessed with the help of the Shapiro–Wilk test. Equality of dispersions of characteristics distribution was assessed with the F-test. In case the distribution was not normal the data was presented through median and interquartile range: Me (Q1; Q3). Mann–Whitney test helped determine significance of differences between groups when comparing independent samples. Comparison of several independent groups benefited from Kruskal–Wallis H test followed by pairwise comparison of the groups using Mann-Whitney test with Bonferroni correction. Comparison of outcomes frequency was done with calculated relative risk and 95 % confidence intervals. Rejection of the null hypothesis occurred at a threshold level of statistical significance of $p = 0.05$.

RESULTS

Immunological ineffectiveness of ART

The incidence of immunological ineffectiveness of ART (II of ART) was 74 (22 %) within a 3-year period. We analyzed the timing of emergence of II of ART and dynamics of CD 4^+ T-lymphocytes growth in the future. In the first year, 48 patients of 341 patients (14 %) did not respond to ART, in the second — 41 of 261 (15.7 %), in the third — 31 out of 195 (15.9 %). See table 1 for data on dismissal of patients from the study.

Of the 48 patients that showed no response to ART in the first year, 24 remained unresponsive in the second year 24 (Fig. 2), 12 did show a response and 12 people were dismissed from the study. In addition, 17 more patients joined II of ART group in the second year. Earlier, these patients enjoyed adequate recovery of $CD4^+$ T-lymphocytes. Of these, 9 people did not respond to treatment in the third year. Thus, a significant portion of patients with II of ART (66.7 %) in the second and third years of treatment were patients that had immunological ineffectiveness of therapy developed in the first year.

During the 1st year of ART, the increase in number of $CD4^+$ T-lymphocytes was: 1) 1 (–25; 22) cells/μL in the group that showed II of ART in both the first and the second years of therapy; 2) 8 (–30; 17) cells/μL in the group that showed II of ART IN the first year and an effective restoration of $CD4^+$ T-lymphocytes numbers in the second year; 3) 102 (77; 156) cells/μL in the group that showed II of ART in the second year only; 4) 165 (83; 263)cells/μL in the group that responded to treatment both in the first and the second years of therapy ($H = 80.6$ at $p < 0.001$; $p_{12} = 0.988$; $p_{13} < 0.001$; $p_{14} < 0.001$; $p_{23} < 0.001$; $p_{24} < 0.001$; $p_{34} = 0.125$).

Of the 195 patients who were followed throughout the study, 12 (6 %) showed no response to the therapy throughout all three years ("absolute nonresponders"); 27 (13.8 %) did not respond to therapy at this or that stage of treatment ("relative nonresponders").

Virological ineffectiveness of ART

Table 1 shows that in the two years of treatment, ART was virologically ineffective (VI of ART) in 25 patients (7.3 %). Second

Table 1. Reasons for patients dismissal from the study

Reason for dismissal	Number of dismissed patients at different stages of ART							
	1st year of ART		2nd year of ART		3rd year of ART		3 years of ART. total	
	abs.	rel.. %	abs.	rel.. %	abs.	rel.. %	abs.	rel.. %
Unauthorized cessation of ART	–	–	19	5.6	11	3.2	30	8.8
Virological ineffectiveness of ART	–	–	18	5.3	7	2.1	25	7.3
Start of AVT	–	–	16	4.7	8	2.3	24	7.0
Death	–	–	7	2.1	5	1.5	12	3.5
Relocation to another region	–	–	6	1.8	2	0.6	8	2.3
Insufficient follow-up period	–	–	14	4.1	33	9.7	47	13.8
Total	–	–	80	23.5	66	19.4	146	42.8

Note. ART — antiretroviral therapy, AVT — antiviral therapy (hepatitis).

year saw more patients not responding to ART's antivirus functions than the first one: 18 patients (5.3 %) against 7 (2.0 %), espectively. For 20 (80.0 %) of 25 patients, ART was VI due to violations of regimens. Once they were helped in making a habit of taking medicines as is proper, the viral load became undetectable again and there was no need to change the regimen. For 5 (20 %) patients, picking the optimal ART regimen took studying drug-resistance of HIV. One patient had less than 1000 copies/ml of HVA RNA so picking the regimen for him was not possible. In 2 patients, the virus showed no resistance to drugs so they received further counseling aimed at forming a habit of taking medicines as prescribed. The remaining 2 patients had HIV resistant (multiple resistance) to NRTIs and NNRTIs, which made it necessary to change their regimens. Thus, VI of ART that resulted from resistance of the virus to drugs was registered in 2 (0.6 %) participants in the study.

34 patients had virus resistance to drugs analyzed before the start of ART (Table 2). 3 patients showed resistance to two classes of drugs (NRTIs/NNRTIs — 1, NRTI/PI — 2), 2 patients — to one (NNRTI). All patients with multi-resistant viruses were previously treated with drugs of the aforementioned classes, to no effect. Patients with resistance to just one class of drugs never received ART before but got the virus from partners for whom ART was VI. At that, only one patient was proved to have cross-resistant virus.

Thus, lax attitude patients show towards treatment regimens contribute significantly to ART's virological ineffectiveness. Patients for whom treatment was VI before tend to have multiple resistant viruses before the start of ART.

Clinical ineffectiveness of ART

30 patients (9 %) had HIV progressing in spite of ART. For more than half of them (62.5 %) the therapy was II. 7 patients (23 %) died due to this progression and a developed disease. Table 3 shows variants of clinical progression.

The majority of patients for whom ART was CI (clinically ineffective) had tuberculosis in 1–4 years of therapy. In 11 (61 %) cases tuberculosis was associated with ART being II. The average content of $CD4^+$ T-lymphocytes (M ± SD) associated with clinical progression of HIV in the form of TB is 277 ± 194 cells/μL, with the minimum value being 25 cells/μL and maximum — 616 cells/μL. The average content of $CD4^+$ that invited herpes infection was 262 ± 81 cells/μL, minimum and maximum values are 174 and 375 cells/μL, respectively. For Candida esophagitis, the average content of $CD4^+$ was 96 ± 41 cells/μL, for oral hairy leukoplakia — 296 cells/μL, for cryptococcosis — 63 cells/μL, for lymphoma — 13 cells/μL.

II of ART made the risk of clinical progression of HIV 6.232 times higher (95 % CI 3.106–12.51).

13 patients died during the study. Among the causes of death, TB is the leader (5 people, or 38 %), followed by diseases CVD (3 people, 23 %). The rest of the deaths were due to cryptococcosis, cirrhosis, cancer, accidents and suicide (one case). Half of the deceased patients (7 cases, 54 %) were "clinical progressors" with ART applied as prescribed. The risk of death for patients that showed no immunological response to ART was 18.6 %, while those for whom the therapy was effective ad this risk at 1.3 %. When assessing immunological ineffectiveness of ART as a death risk factor, it was found that II of ART increased patient's chances of dying 13.8 times compared to patients that had an effective increase in the number of $CD4^+$ T-lymphocytes as a result of therapy ($p < 0.001$; 95 % CI 4.359–44.07). At that, the risk of dying AIDS was 36.8–times higher ($p < 0.001$; 95 % CI 4.42–307.6).

DISCUSSION

We have found that over 3 years, ART can be II in 22 % of cases. This is greater than Russian [6] and foreign [3] colleagues reported earlier. However, considering just 1 year we received comparable results: ART was II in 14, 15.7, and 15.9 % of cases in our study, while Shmagel et al. report 11.3 % [6] and Moore et al. — 15 % [3]. To make accurate assessments, we need to monitor patients receiving ART for a long period of time because every year there may be more patients that do not respond to the therapy.

For some reason, some patients with "good" immunological response in the first year of ART did not have the number of $CD4^+$ T-lymphocytes restoring in the following years of therapy. It may be connected to peculiarities of ART regimen [7]. Another possible reason is the development of secondary diseases in the second or third years of ART, diseases that hinder restoration of $CD4^+$ number [8]. However, in the context of our study only 3 of 17 patients for whom ART was II showed clinical progression of HIV in the second year of treatment. Perhaps, the II criteria we have suggested for the 1st year of treatment should be different, i. e. the treatment can be considered effective in case there is a more pronounced immune response than 50 more $CD4^+$ cells a year [9, 10]. $CD4^+$ cells numbers increase in the course of one year of therapy indicates that addition of more than 100 cells/μL within the 1st year enhances immunologic success of the therapy, and if the number is less than 50 cells/μL, in most cases (but not always) further restoration of T-lymphocytes will be ineffective.

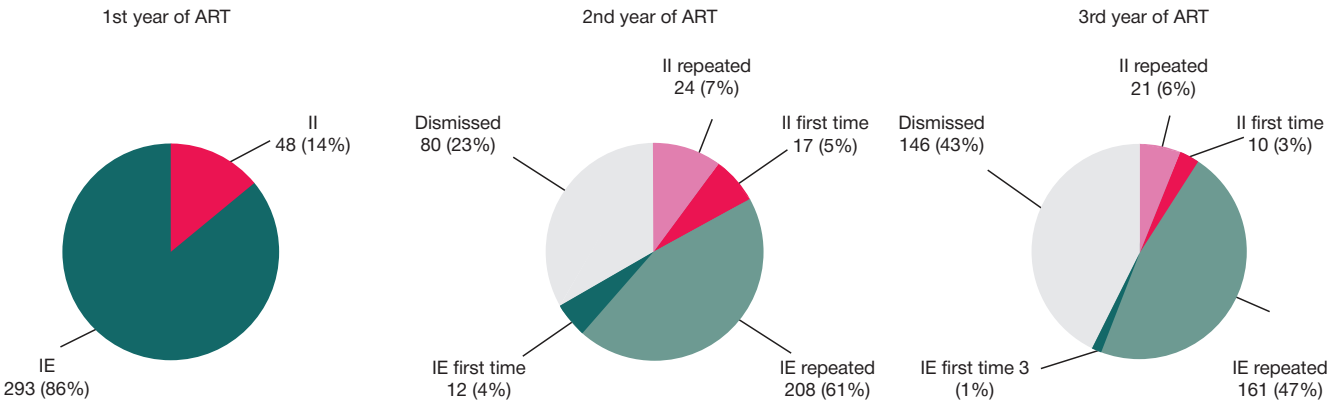

Fig. 2. Groups of patients by immunological response to ART (II — immunological ineffectiveness, IE — immunological effectiveness)

Table 2. HIV resistance to antiretroviral drugs, test results (n = 34)

HIV resistance to ART	Number of patients with HIV resistant to ART drugs.																		
Detected	5 (15 %)																		
	NRTIs							NNRTIs				PI							
	AZT	3TC	ABC	TDF	FTC	ddI	d4T	EFV	NVP	ETR	DLV	LPV/r	DRV	ATV	SQV	FPV	IDV	NFV	TPV
	2	3	2	1	3	2	1	2	2	–	1	1	–	2	1	1	1	1	–
Not detected	29 (85 %)																		

Note. ART — antiretroviral therapy; NRTIs — nucleoside reverse transcriptase inhibitor; NNRTI — non-nucleoside reverse transcriptase inhibitor; PI — protease inhibitor; AZT — azidothymidine; ABC — abacavir; 3TC — lamivudine; TDF — tenofovir; FTC — emtricitabinum; ddI — didanosinum; d4t — stavudinum; EFV — efavirenz; NVP — nevirapine; ETR — etravirine; DLV — delavirdine; LPV/r — lopinavir boosted with ritonavir; DRV/±r — darunavir boosted/not boosted with ritonavir; ATV — atazanavirum; SQV — saquinavirum; FPV — fosamprenavirum; IDV — indinavirum; NFV — nelfinavirum; TPV — tipranavirum.

Table 3. Variants of clinical progression of HIV with ongoing ART (n = 30)

Disease	HIV progression cases at various stages of ART									
	Total		1st year of ART		2nd year of ART		3rd year of ART		4th year of ART	
	abs.	rel., %	abs.	rel., %	abs.	rel., %	abs.	rel., %	abs.	rel., %
Tuberculosis	18	60	5	17	7	23	3	10	3	10
Herpetic infection	7	23	6	20	1	3	–	–	–	–
Candidiasis	3	10	3	10	–	–	–	–	–	–
Oral hairy leukoplakia	1	3	1	3	–	–	–	–	–	–
Cryptococcosis	1	3	1	3	–	–	–	–	–	–
Lymphoma	1	3	1	3	–	–	–	–	–	–
Total	31	103	17	57	8	27	3	10	3	10

100 cells/μL can be considered a borderline level at which it is not possible to predict immunological effectiveness of ART.

It should be noted here that virological effectiveness of treatment for at least the first year was the inclusion criterion, thus there no cases of VI of ART for that period of time to report. Virological effectiveness of ART in the second and third years of therapy was 92.7 %, which coincides with the data foreign authors report for a similar period of observation [11]. Same as in other studies, ART was VI mostly due to violation of regimen (80 % of cases in our study, 56 % — in the study by Klein et al. [12]). Only 8 % of patients that took part in our study and 9 % of the patients reported on in Klein's study had virus resistant to drugs. Initial drug-resistant HIV was detected in 5 of 34 study participants tested for such resistance. This justifies the need for testing for virus' drug resistance prior to start of ART, especially if the patient has had ART VI previously and/or was infected by a partner with drug-resistant HIV. The testing should allow choosing the optimal treatment regimen.

The share of "clinical progressors" with ART ongoing was quite high: 9 %. The majority of patients had tuberculosis in 1–4 years of therapy. 61 % of cases were associated with ART being II. We believe that TB could produce an adverse effect on the development of II of ART, because one-third (36.5 %) of study participants whose immune system did not respond to ART were ill with tuberculosis that developed either before the start of ART (22 % of patients with II of ART) or during ART (15 % of patients with II of ART), whereas the incidence of tuberculosis among patients for whom ART was effective equaled 12 % ($p < 0.001$). Other variants of clinical progression of HIV mainly occurred in the first year of ART. This is probably due to the general TB situation in Russia, which is adverse, and the threshold $CD4^+$ T-lymphocytes number that allows emergence of opportunistic infections. On the one hand, development of new secondary diseases when the number of $CD4^+$ grows is undesirable since it is associated with an increased risk of death and greater cost of treatment. On the other hand, such a development signals that the immune system is restoring with ART in the background. The average content of $CD4^+$ T-lymphocytes associated with clinical progression of HIV in the form of TB is 277 ± 194 cells/μL. This means that avoiding clinical progression requires starting ART early, when the content of $CD4^+$ is > 350 cells/μL, and prevention of secondary diseases (especially tuberculosis).

As for the risk of clinical progression of HIV infection when ART is II, the value we got, which is 6.232 times greater risk (95 % CI 3.106–12.51), is in the middle between the values other researchers reported [2, 3].

CONCLUSIONS

We have found that ART is II in 14.0–15.9 % of cases over one year and in 22 % of cases over 3 years. Of the 195 people that participated in the study from start to finish, 12 patients (6 %) showed ART II throughout all the years of treatment. It was noted that the number of cases of ART being II increases slightly from the first to the third year of treatment, and it is largely determined by the number of patients that had ART II after the first year of treatment. Adequate growth of $CD4^+$ T-lymphocytes after the first year of treatment requires the cells to grow their numbers by more than 100 cells/μL during the first year. This level can be used practically as an indicator of immunological effectiveness of ART for timely correction of treatment.

Virological effectiveness of ART was 92.7 % through two years. Ineffective viral load suppression was observed in 6.0 % of cases ad resulted from violation of regimen by patients. Only 0.6 % of cases were VI due to virus' drug resistance. Thus, proper attention to counseling aimed at forming a habit of sticking to the regimen can significantly improve virologic effectiveness of the treatment. The identified the original drug resistance of the virus (15 %) was associated with previous ART failures or infection from a partner with a drug-resistant virus. This fact necessitates testing this category of patients for HIV resistance to antiretroviral drugs before starting ART.

Clinical effectiveness of ART was 91 %. This result largely depends on the number participants for whom ART was II. TB was a leading disease clinical progression of HIV resulted in (61 % of cases). It is associated with a wide spread of values of content of $CD4^+$ T-lymphocytes (25–616 cells/μL), which signals the need for an earlier start of ART, when $CD4^+$ content is at > 350 cells/μL, and prevention of secondary diseases.

II of ART is a risk factor, the risk being progression of the disease with active ART in the background and death of the HIV-positive individual. This fact confirms the need for timely recognition of II and treatment regimen correction.

References

1. Grabar S, Le Moing V, Goujard C, Leport C, Kazatchkine MD, Costagliola D, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. Ann Intern Med. 2000 Sep 19; 133 (6): 401–10.
2. Piketty C, Weiss L, Thomas F, Mohamed AS, Belec L, Kazatchkine MD. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a proteas inhibitor-containing regimen. J Infect Dis. 2001 May 1; 183 (9): 1328–35.
3. Moore DM, Hogg RS, Yip B, Wood E, Tyndall M, Braitstein P, et al. Discordant immunologic and virologic responses to highly active antiretroviral therapy are associated with increased mortality and poor adherence to therapy. J Acquir Immune Defic Syndr. 2005 Nov 1; 40 (3): 288–93.
4. Gilson RJ, Man SL, Copas A, Rider A, Forsyth S, Hill T, et al. Discordant responses on starting highly active antiretroviral therapy: suboptimal CD4 increases despite early viral suppression in the UK Collaborativ HIV Cohort (UK CHIC) Study. HIV Med. 2010 Feb; 11 (2): 152–60.
5. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01 [software], updated 2013 Apr 06 [cited 2017 Feb 03]. Available from: http://www.openepi.com/Menu/OE_Menu.htm.
6. Shmagel K, Shmagel N. Restoration of the number of CD4+ lymphocytes on different antiretroviral medicines and HAART regimens [abstract]. Proceedings of the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2011 July 17–20; Rome, Italy. CDB331.
7. Huttner AC, Kaufmann GR, Battegay M, Weber R, Opravil M. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. AIDS. 2007 May 11; 21 (8): 939–46.
8. Merlini E, Bai F, Bellistrì GM, Tincati C, d'Arminio Monforte A, Marchetti G. Evidence for Polymicrobic Flora Translocating in Peripheral Blood of HIV-Infected Patients with Poor Immune Response to Antiretroviral Therapy. PLoS One. 2011 Apr 11; 6 (4): e18580.
9. Kaufmann GR, Furrer H, Ledergerber B, Perrin L, Opravil M, Vernazza P, et al. Characteristics, determinants, and clinical relevans of CD4 T cell recovery to <500 cell/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis. 2005 Aug 1; 41 (3): 361–72.
10. Kelley CF, Kitchen CM, Hunt PW, Rodriguez B, Hecht FM, Kitahata M, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. Clin Infect Dis. 2009 Mar 15; 48 (6): 787–94.
11. Singini I, Campbell TB, Smeaton LM, Kumarasamy N, La Rosa A, Taejareonkul S, et al. Predictors of late virologic failure after initial successful suppression of HIV replication on efavirenz-based antiretroviral therapy. HIV Clin Trials. 2016 Jul 29; 17 (5): 173–80.
12. Klein A, Vogel M, Schwarze-Zander C, Rockstroh J, Wasmuth J-C. Why not below the limit of detection? An analysis of the Bonn HIV cohort [abstract]. Proceedings of the EACS — 12th European AIDS Conference; 2009 Nov 11–14; Cologne, Germany. PE7.4/4.

Литература

1. Grabar S, Le Moing V, Goujard C, Leport C, Kazatchkine MD, Costagliola D, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. Ann Intern Med. 2000 Sep 19; 133 (6): 401–10.
2. Piketty C, Weiss L, Thomas F, Mohamed AS, Belec L, Kazatchkine MD. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a proteas inhibitor-containing regimen. J Infect Dis. 2001 May 1; 183 (9): 1328–35.
3. Moore DM, Hogg RS, Yip B, Wood E, Tyndall M, Braitstein P, et al. Discordant immunologic and virologic responses to highly active antiretroviral therapy are associated with increased mortality and poor adherence to therapy. J Acquir Immune Defic Syndr. 2005 Nov 1; 40 (3): 288–93.
4. Gilson RJ, Man SL, Copas A, Rider A, Forsyth S, Hill T, et al. Discordant responses on starting highly active antiretroviral therapy: suboptimal CD4 increases despite early viral suppression in the UK Collaborativ HIV Cohort (UK CHIC) Study. HIV Med. 2010 Feb; 11 (2): 152–60.
5. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01 [software], updated 2013 Apr 06 [cited 2017 Feb 03]. Available from: http://www.openepi.com/Menu/OE_Menu.htm.
6. Shmagel K, Shmagel N. Restoration of the number of CD4+ lymphocytes on different antiretroviral medicines and HAART regimens [abstract]. Proceedings of the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2011 July 17–20; Rome, Italy. CDB331.
7. Huttner AC, Kaufmann GR, Battegay M, Weber R, Opravil M. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. AIDS. 2007 May 11; 21 (8): 939–46.
8. Merlini E, Bai F, Bellistrì GM, Tincati C, d'Arminio Monforte A, Marchetti G. Evidence for Polymicrobic Flora Translocating in Peripheral Blood of HIV-Infected Patients with Poor Immune Response to Antiretroviral Therapy. PLoS One. 2011 Apr 11; 6 (4): e18580.

9. Kaufmann GR, Furrer H, Ledergerber B, Perrin L, Opravil M, Vernazza P, et al. Characteristics, determinants, and clinical relevans of CD4 T cell recovery to <500 cell/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis. 2005 Aug 1; 41 (3): 361–72.
10. Kelley CF, Kitchen CM, Hunt PW, Rodriguez B, Hecht FM, Kitahata M, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. Clin Infect Dis. 2009 Mar 15; 48 (6): 787–94.
11. Singini I, Campbell TB, Smeaton LM, Kumarasamy N, La Rosa A, Taejareonkul S, et al. Predictors of late virologic failure after initial successful suppression of HIV replication on efavirenz-based antiretroviral therapy. HIV Clin Trials. 2016 Jul 29; 17 (5): 173–80.
12. Klein A, Vogel M, Schwarze-Zander C, Rockstroh J, Wasmuth J-C. Why not below the limit of detection? An analysis of the Bonn HIV cohort [abstract]. Proceedings of the EACS — 12th European AIDS Conference; 2009 Nov 11–14; Cologne, Germany. PE7.4/4.